REMARKS

Rejections Under 35 USC §103(a)

Claim 6 stands rejected under 35 U.S.C. §103(a) as being unpatentable over **Hallahan** (U.S. Patent No. 6,159,443) in view of WO 98/53852, the known fact disclosed in the specification on page 4, lines 3-20; page 5, lines 1-5; and page 10, lines 12-20, and **Mastrobattista** et al. (Biochim. Biophys. Acta. 1419:353-363 (1999)) and **Patel** et al. (FASEB 12:1447-1454 (1998)). This rejection is respectfully traversed.

Claim 6 is drawn to a method of using irradiation and particles of biodegradable polymers or PEGylated copolymers comprising antibodies or antibody fragments that bind to ICAM-1 expressed on endothelial cells to treat cancer in an individual.

The Examiner states that **Hallahan** teach a method of treating cancer by exposing a target tissue or organ to ionizing radiation and administering P-selectin antibody labeled delivery vehicle that carry active agent to the tumors (Abstract; col. 6, lines 5-30; col. 13, lines 24-30). The Examiner also argues that **Hallahan** teach a radiation-induced increase in P-selectin in irradiated tumor,

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and that the use of radiation to control cellular adhesion molecules is a unique approach to treatment of tumors (col. 6, lines 5-15).

The Examiner argues that WO 98/53852 teaches exposing tissue to irradiation causes an increase in expression of several cell adhesion molecules including ELAM-1, E-selectin and ICAM-1 in endothelial cells (pg. 2, lines 15-25; pg. 3, lines 1-10).

The Examiner argues that the known fact disclosed in the specification on page 4, lines 3-20; page 5, lines 1-5; and page 10, lines 12-20 teach that it has been known for 15 years that exposure of normal and diseased tissue to irradiation causes an increase of leukocyte infiltration and adhesion of leukocytes to microvascular endothelium.

The Examiner argues that **Mastrobattista** et al. teach biomolecular carrier bearing anti-ICAM-1 antibodies, and the uses of anti-ICAM-1 immunoliposomes *in vitro*. **Patel** et al. teach particles of biodegradable polymer or PEGylated copolymer as a new type of drug carrier.

The Examiner contends that it would have been obvious to apply the teaching of WO 98/53852, the known fact disclosed in

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the specification, **Mastrobattista** et al. and **Patel** et al. to those in **Hallahan** and substitute biomolecular carrier bearing antibodies to one cellular adhesion molecule, i.e. P-selectin, to antibodies against another cellular adhesion molecule, i.e. ICAM-1. Applicant respectfully disagrees.

To establish obviousness, all of the elements of the invention must be taught by the combination of the prior art. Applicant submits that the cited references do not teach all of the elements of the present invention. Specifically, Applicant submits that the combined cited references do not teach *in vivo* targeting of ICAM-1 expressed on the surface of endothelial cells. **Hallahan** teaches P-selectin which is localized to the vascular lumen and not on the vascular endothelial cell surface in irradiated tumors *in vivo* (col. 5, line 64 to col. 6, line 45). The uses of anti-GP-IIb or anti-GP-IIIa antibodies "revealed the P-selectin is of platelet, not endothelial, origin" (col. 6, lines 7-9). On the other hand, **Mastrobattista** et al. only teach the uses of anti-ICAM-1 immunoliposomes *in vitro*. Hence, taken together, the cited references only teach targeting non-endothelial cell antigen *in vivo* or targeting ICAM-1 *in vitro*.

Moreover, Applicant submits that the combined

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teachings of the cited references do not provide one of ordinary skill in the art with a reasonable expectation of successfully producing Applicant's invention. As discussed above, the combined references only teach targeting ICAM-1 *in vitro*; the combined references do not teach targeting endothelial cell surface antigen ICAM-1 *in vivo*. Results from *in vitro* experiments do not provide any reasonable expectation of successfully targeting ICAM-1 *in vivo*. Whether anti-ICAM-1 antibodies can be used to target tumor tissue *in vivo* has to be determined by actual experimentation because ICAM-1 is expressed on cell types, e.g. leukocytes, other than endothelial cells in tumor tissue. A reasonable expectation of success must be found in the combination of cited references and not from Applicants' disclosure. Applicants demonstrated that no adhesive interactions between anti-ICAM-1 coated microspheres and leukocytes occurred *in vivo* (pg. 28, ll. 1-12). *In vitro* experiments do not provide any indication on whether anti-ICAM-1 antibodies administered *in vivo* will be diverted away from target tissue and bind to other ICAM-1-expressing cells. Thus, the feasibility of targeting ICAM-1 *in vivo* by anti-ICAM-1 antibodies has to be determined by empirical experimentation.

The cited references do not provide any data relevant to

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in vivo targeting of ICAM-1 by anti-ICAM-1 antibodies. The *in vivo* data reported in **Hallahan** are not relevant to *in vivo* targeting of ICAM-1. **Hallahan** only teaches targeting of non-endothelial cell antigen P-selectin which is localized to the vascular lumen, not on vascular endothelial cell surface in irradiated tumors *in vivo* (**Hallahan**, col. 5, line 64 to col. 6, line 45). P-selectin and ICAM-1 have different expression patterns and different cellular localization. Successful targeting of P-selectin may provide reasonable expectation of success on targeting antigens that have similar expression pattern and cellular localization. Targeting of P-selectin, however, does not indicate whether similar targeting would be observed on another antigen that has different cellular expression and localization patterns. As discussed above, whether anti-ICAM-1 antibodies can be used to target tumor tissue *in vivo* has to be determined by actual experimentation.

In view of the above remarks, the combined teaching of the cited references do not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicant's claimed methods. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the

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invention was made. Accordingly, Applicant respectfully requests that the rejection of claim 6 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Final Office Action mailed August 25, 2004. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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